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09/869,106	10/09/2001	Isabelle Poquet	045636-5048	1150

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EXAMINER
GRASER, JENNIFER E

ART UNIT	PAPER NUMBER
1645	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/869,106	Applicant(s) Poquet et al.
	Examiner Jennifer Graser	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Election & Amendt. B, 4/21/03*

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-23* is/are pending in the application.

4a) Of the above, claim(s) *19-22* is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-18 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, claims 11-16 in Paper No. 10B is acknowledged. The traversal is on the ground(s) that amendment of the claims in the Response to the Restriction Requirement to recite the common technical special feature of a gram positive bacteria that does not express a functional HtrA protease has necessitated that the claims be regrouped into one group. This has been found persuasive with respect to claims 17, 18 and 23 and they will be placed in Group I and examined. However, claims 19-22 are drawn to methods which produce three different products, i.e., a fermented product, a dietetic food and a medicinal product. These three methods which produce completely different products lack unity of invention with one another and the elected group as they are drawn to producing three completely different products, i.e, three different special technical features- a medicinal product, a fermented product and a dietetic food.

Claims 11-18 and 23 are currently under examination. Claims 19-22 have been withdrawn from examination because they are drawn to a non-elected invention.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 11-18 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is vague and indefinite because it is unclear what is meant by the term "HtrA protease". What does 'HtrA'stand for? Does it refer to a specific individual HtrA protease such as the one which is produced by *E.coli* or *Salmonella* or does it stand for something else? Further, not many Gram positive strains produce a protease known as 'HtrA'. Additionally, this claim reads on any Gram positive bacterium which is not known to naturally produce a HtrA protease. Accordingly, any naturally occurring Gram positive bacterium which is not known to produce a HtrA protease, such as *Corynebacterium or Staphylococci*, would read on the claim. The description in the claim is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. Clarification is requested.

Claim 18 is vague and indefinite because it is unclear if the "PtrP protease" mentioned is in addition to the 'HtrA protease' mentioned in the claim from which it depends or if Applicants are referring to the fact that 'PtrP' is a homolog of the 'HtrA' protease. Clarification is requested.

Claims 11 and 16 are vague and indefinite because it is unclear what is meant by the term "HtrA protease". What does 'HtrA'stand for? Does it refer to a specific individual HtrA protease such as the one which is produced by *E.coli* or *Salmonella* or does it stand for

something else? Further, not many Gram positive strains produce a protease known as 'HtrA'. Clarification is requested.

Claim 13 is vague and indefinite because the prior art teaches that the only Gram positive bacterium which produces a "HtrA' protease is *Lactobacillus*. Accordingly, it is unclear if Applicants intend to also mean 'homologs' of HtrA. Clarification is requested.

Claim 15 is vague and indefinite because it is unclear if the "PtrP protease" mentioned is in addition to the 'HtrA protease' mentioned in the claim from which it depends or if Applicants are referring to the fact that 'PtrP' is a homolog of the 'HtrA' protease. Clarification is requested.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 23 and 11-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Bayles et al. (Abstracts of the 97th General Meeting of the ASM. May 4-8, 1997. Miami).

Bayles et al teach a Gram positive bacterial strain, *Listeria monocytogenes*, which does not express a functional HtrA protease. The mutant *Listeria* bacterial strain taught by Bayles et al is defective in a *degP* (HtrA) homolog. The reference teaches that sequence analysis revealed that a transposon was inserted into a gene which is homologous to the carboxy-terminal portion

of a putative *Bacillus subtilis* serine protease. It is taught that this serine protease has a high degree of homology to the heat shock protein DegP(HtrA) of *Salmonella typhyimurium.* This bacterium also does not produce a functional PtrP protease so it meets the requirements of claim 18. The method recited in instant claims 11-15 only requires culturing the Gram positive bacterial strain and since this is inherent in the reference the claims are anticipated.

6. Claim 23 and 11-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Buist et al (J. Bacteriol. November 1998, 180(22): 5947-5953). It is noted that the absolute priority of the present application is to foreign application FR 98/16462 so prior art published one day before Dec. 24, 1998 qualifies as 102(b) art.

Buist et al teach that Gram positive bacterial strains which do not express functional proteinases were well known in the art for many years. On page 5947, col.2, it is noted that Jolliffe et al. 1980. taught multiple proteinase-deficient strains of *B.subtilis.* It is also noted that Coxon et al. 1991. showed that protease deficiency of *B.subtilis* was associated with an increased tendency of cells to lyse as they approach stationary phase. Buist et al teach a PtrP-negative strain of *L.lactis*. See page 3948, column 2. They also teach that, as expected, protease activity was absent in the cell extract and supernatant of this PtrP-negative strain. PtrP is a homolog of HtrA. Since it is unclear what is intended by the term 'HtrA' in the instant claims it is being interpreted as including homologs of the HtrA protease. The method recited in instant claims 11-15 only requires culturing the Gram positive bacterial strain and since this is inherent in the reference the claims are anticipated. method.

7. Claim 23 and 11-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Smeds et al. (J.Bacteriol. Dec. 1998. 180(23): 6148-6153).

Smeds et al teach a strain of *Lactobacillus helveticus* which does not produce a functional HtrA protease. Smeds et al created a mutant *L.helveticus* by replacing the 5' end of *htrA* with the *gusA* reporter gene. The fusion of the *gusA* gene was downstream of the stress-inducible *htrA* promoter and disrupted the *htrA* gene. See page 6150, column 1. The method recited in instant claims 11-15 only requires culturing the Gram positive bacterial strain and since this is inherent in the reference the claims are anticipated.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 16, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bayles et al or Buist et al, as applied to claims 23 and 11-15 above, and further in view of any one of Dougan et al (WO 91/15572) or Georgiou et al (US 5,264,365).

The teachings of Bayles and Buist are set forth above. However, they do not particularly exemplify the use of their htrA mutant strains for recombinantly producing a protein of interest wherein the method includes introducing into the bacterial strain a nucleic acid sequence encoding a protein of interest operably linked to a promoter, wherein the nucleic acid is not

integrated into a gene encoding the HtrA protease; and culturing the bacterial strain under conditions causing expression of the protein from the nucleic acid.

Dougan et al teach a method of expressing a heterologous antigen in a bacterial strain which is an htrA mutant, i.e., one that cannot express a functional htrA protease. See page 7, first full paragraph. It is specifically taught that an expression cassette may be used to produce the htrA mutant bacterial strain. See page 7, second full paragraph. Georgiou et al teaches teach protease-deficient *E.coli* hosts which when combined with an expression system are useful for the production of proteolytically sensitive polypeptides. See abstract. Georgiou et al also teaches that the use of an inducible expression system with a constitutively protease-deficient bacterial host strain was known in the art to solve the problem of low polypeptide production in bacterial host cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the PrtP/htrA(d*egP)* mutants taught by Bayles or Buist to recombinantly produce a heterologous protein (protein of interest) because both Dougan and Georgiou teach that it was well known in the art to use protease mutants as host cells for producing proteins of interest because they will not act upon polypeptides to effect degradation and because the expression of heterologous proteins is likely to be more favorable in htrA mutants because of the increased stability of recombinant antigens associated with the degP phenotype (see Dougan page 7, first full paragraph). One of ordinary skill in the art would be especially motivated to use the strains of Bayles or Buist for protein production because they

would be expected to get a greater protein yield in the protease mutants and encounter more stability.

Prior art made of record:

Vos et al (WO 91/02064) Modified Proteases and their use in Foodstuffs.

Friesland et al (WO 97/38587) Methods for Producing Dairy Products, in Particular Cheese using Lactic Acid bacteria provided with additional Neutral Protease Activity.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JGraser

JENNIFER E. GRASER
PRIMARY EXAMINER
6/9/03